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Increasing High Density Lipoprotein Cholesterol (HDL) by CETP-Inhibition – a rocky road and lessons learned ?

The early demise of the dal-HEART programme

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Raising the level of HDL cholesterol has been proposed as a potential therapeutic strategy to reduce cardiovascular risk, largely based on the epidemiological studies showing that low HDL cholesterol levels are associated with an increased risk of coronary disease and cardiovascular events (1, 2) this has been supported by experimental as well as translational studies which has demonstrated anti-atherogenic properties of HDL (3). This led to the perception of HDL cholesterol as the “good cholesterol”. Notably, in the Treating to New Targets (TNT) study, low HDL cholesterol levels remained a marker of increased cardiovascular risk even in coronary patients with low LDL cholesterol levels (< 70 mg per deciliter) on statin therapy (2).

While initial studies proposed reverse macrophage cholesterol transport by HDL as the main anti-atherogenic mechanism (4), more recent studies highlighted endothelial-protective properties of HDL, including stimulation of endothelial nitric oxide (NO) production, as well as anti-inflammatory, anti-apoptotic and anti-thrombotic effects (5, 6). Importantly, however, these studies have used HDL isolated from healthy subjects or reconstituted HDL which differ in several ways from HDL obtained from patients with coronary disease, as discussed below.

Inhibition of cholesteryl ester transfer protein (CETP) offers an unprecedented opportunity to increase profoundly HDL cholesterol plasma levels (7). This has resulted in several large scale programs to explore the potential of CETP as a novel therapeutic target for cardiovascular prevention. The large randomized ILLUMINATE trial examined the effects of the CETP inhibitor torcetrapib on clinical outcomes in 15,067 patients at high cardiovascular risk. In spite of a marked increase in plasma HDL cholesterol levels of 72.1 %, the trial had to be stopped due to increased mortality and morbidity in the treatment group (8). In subsequent mechanistic studies, the adverse effects of torcetrapib were attributed to off-target toxicity, in particular increased production of aldosterone as well as an increased production of endothelin and reduced expression of endothelial nitric oxide synthase in the vessel wall (9). These off-target effects of torcetrapib were held responsible for the observed increase in arterial blood pressure with this agent (8). Two posthoc analyses, the first in ILLUMINATE and the second in ILLUSTRATE, the coronary IVUS study with torcetrapib, indicated that those participants with the highest increase of HDL cholesterol or achieved on-treatment HDL cholesterol levels did

show cardiovascular benefit. This raised hopes that other CETP inhibitors without the off-target toxicity of torcetrapib would lead to prevention of recurrent events (8, 10, 11).

The dal-HEART program was a carefully designed clinical development program of another CETP inhibitor, dalcetrapib, that to the surprise of many was stopped on Saturday, 5th May 2012. The interim analysis of the large phase-3 dal-OUTCOMES trial, involving more than 15'600 patients with recent acute coronary syndrome, had revealed lack of efficacy in reducing cardiovascular events (12). This clinical trial program was the first development program of a CETP inhibitor after the torcetrapib failure. With this experience in mind, two safety studies, the dal-VESSEL and the dal-PLAQUE studies, designed to exclude adverse vascular effects of the compound, were part of the early development programme (13, 14). Whereas both studies did not reveal adverse vascular effects of dalcetrapib therapy neither on endothelial function as assessed by flow-mediated dilation nor on vascular structure as examined by carotid MRI, there was also not a convincing signal that the compound would exert protective effects on these parameters (13, 14).

Indeed, inspite of a marked increase in HDL cholesterol plasma levels by 30% and a lack of effect on blood pressure, endothelial function was not improved (as had been the case with reconstituted HDL. (15)) Similarly, despite a suggestion of potential benefit plaque size and inflammation (as assessed by positron emission tomography using fluoro-desoxyglucose as tracer) were largely affected by the drug. Unfortunately, these findings had received little attention, although they now appear in strong agreement with the neutral outcome of the phase-3 clinical trial.

Another more potent CETP inhibitor, anacetrapib, is currently developed by Merck and is being tested in a large phase 3 clinical program (see ClinicalTrials.gov Identifier: NCT01252953) after the long-term safety study DEFINE revealed encouraging results on blood pressure and lipids (16). Furthermore, Eli Lilly's evacetrapib has also entered a clinical trial program (17). While dalcetrapib only increased HDL cholesterol relatively modestly, both anacetrapib and evacetrapib also markedly lower LDL cholesterol, small dense LDL, lipoprotein (a), non-HDL cholesterol and apolipoproteinB, even on top of potent statin therapy (Table). Moreover, a very recent and large Mendelian randomization study has confirmed

that lower CETP activity, when associated with both lower LDL and higher HDL, is associated with cardiovascular benefit (18).

Interpretation and prediction of the impact of CETP-inhibitors is complicated by the growing awareness that the effects of HDL cholesterol may vary in different clinical settings. For example the effects of HDL cholesterol on macrophage cholesterol efflux and in particular the endothelial effects of HDL cholesterol are altered in patients with coronary disease or diabetes as well other inflammatory conditions, a phenomenon referred to as “HDL dysfunction” (3). Indeed, Khera et al. found that the cholesterol efflux capacity of apoB-depleted serum (as a measure of the capacity of HDL to accept cholesterol from macrophages) was inversely related to carotid intima-media thickness and the likelihood of angiographic coronary artery disease independent of the HDL cholesterol plasma levels (19). We have observed that the capacity of HDL to stimulate endothelial NO production and endothelial repair is substantially reduced in patients with coronary artery disease or diabetes mellitus (20, 21). Of note, HDL, isolated from healthy subjects, substantially stimulated endothelial cell NO production and accelerated endothelial repair in vivo, whereas no such or even opposite effects were observed when HDL was isolated from patients with coronary disease or diabetes (20, 21). The underlying mechanisms need to be further defined, but likely include increased lipid oxidation of HDL due to a reduced HDL-associated paraoxonase-1 activity, an enzyme that protects HDL from lipid oxidation, as well as modifications of the protein moiety. HDL is a highly complex lipoprotein that can scavenge more than 70 proteins, as identified by proteomics analysis (22), and may contain more than 1000 different lipid species with each of them being modifiable. The vascular effects of HDL are not necessarily predictable by simply measuring its cholesterol concentration, since cholesterol is only a non-functional cargo of this lipoprotein and hence a surrogate marker reflecting the size and number of HDL particles. These observations raise the possibility that the vascular effects of on-treatment HDL may be an important determinant of the overall cardiovascular benefits of an HDL-raising intervention. Indeed, an increase in the plasma levels of dysfunctional HDL particles by interfering with their catabolism through CETP inhibition may in fact be detrimental. Hence, both the on-treatment vascular effects of HDL as well as the underlying molecular mechanism leading to increased HDL cholesterol levels are likely important determinants of the overall vascular effects of an HDL-cholesterol raising therapeutic

intervention. Thus, targeting HDL cholesterol by CETP inhibition remains a “rocky road”. It appears that we need to learn more about the biology of HDL and its relation to atherosclerotic vascular disease. Notably easy-to-measure biomarkers reflecting HDL functionality better than HDL cholesterol or apoA-I levels are urgently needed. In this regard, *post hoc* analyses of Dal-OUTCOME and its biobank may turn out as a highly valuable resource towards better understanding of the dalcetrapib failure. The extensive dal-HEART program included early safety studies with surrogate measures as an endpoint to detect potential adverse effects of dalcetrapib early on. It is noteworthy that the dal-VESSEL study showed no evidence of adverse vascular effects (similar to those with torcetrapib) but also no evidence of benefit on vascular function. The dal-PALQUE study showed some weak effects on the carotid wall.

Atherosclerosis progress for many years before clinical events and involves dysfunctional vascular biology characterised by inflammation and endothelial dysfunction. In hindsight, the lack of a convincing positive signals from the two studies of function and structure should have been given more weight.

Such studies in the future should perhaps be included in development programs for drugs which target novel mechanisms for atherosclerosis modification and cardiovascular risk reduction.

References

1. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J. Major lipids, apolipoproteins, and risk of vascular disease. *Jama*. 2009;302:1993-2000
2. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, Kastelein JJ, Bittner V, Fruchart JC. Hdl cholesterol, very low levels of ldl cholesterol, and cardiovascular events. *N Engl J Med*. 2007;357:1301-1310
3. Besler C, Luscher TF, Landmesser U. Molecular mechanisms of vascular effects of high-density lipoprotein: Alterations in cardiovascular disease. *EMBO Mol Med*. 2012;4:251-268
4. Tall AR, Yvan-Charvet L, Terasaka N, Pagler T, Wang N. Hdl, abc transporters, and cholesterol efflux: Implications for the treatment of atherosclerosis. *Cell Metab*. 2008;7:365-375
5. Yuhanna IS, Zhu Y, Cox BE, Hahner LD, Osborne-Lawrence S, Lu P, Marcel YL, Anderson RG, Mendelsohn ME, Hobbs HH, Shaul PW. High-density lipoprotein binding to scavenger receptor-bi activates endothelial nitric oxide synthase. *Nat Med*. 2001;7:853-857
6. Mineo C, Deguchi H, Griffin JH, Shaul PW. Endothelial and antithrombotic actions of hdl. *Circ Res*. 2006;98:1352-1364
7. Brousseau ME, Schaefer EJ, Wolfe ML, Bloedon LT, Digenio AG, Clark RW, Mancuso JP, Rader DJ. Effects of an inhibitor of cholesteryl ester transfer protein on hdl cholesterol. *N Engl J Med*. 2004;350:1505-1515
8. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr

- KA, Fisher MR, Tall AR, Brewer B. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;357:2109-2122
9. Simic B, Hermann M, Shaw SG, Bigler L, Stalder U, Dorries C, Besler C, Luscher TF, Ruschitzka F. Torcetrapib impairs endothelial function in hypertension. *Eur Heart J*. 2011
 10. Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT, Ruzyllo W, Bachinsky WB, Lasala GP, Tuzcu EM. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med*. 2007;356:1304-1316
 11. Nicholls SJ, Tuzcu EM, Brennan DM, Tardif JC, Nissen SE. Cholesteryl ester transfer protein inhibition, high-density lipoprotein raising, and progression of coronary atherosclerosis: Insights from illustrate (investigation of lipid level management using coronary ultrasound to assess reduction of atherosclerosis by cetp inhibition and hdl elevation). *Circulation*. 2008;118:2506-2514
 12. Schwartz GG, Olsson AG, Ballantyne CM, Barter PJ, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Shah PK, Tardif JC, Chaitman BR, Duttlinger-Maddux R, Mathieson J. Rationale and design of the dal-outcomes trial: Efficacy and safety of dalcetrapib in patients with recent acute coronary syndrome. *Am Heart J*. 2009;158:896-901 e893
 13. Luscher TF, Taddei S, Kaski JC, Jukema JW, Kallend D, Munzel T, Kastelein JJ, Deanfield JE. Vascular effects and safety of dalcetrapib in patients with or at risk of coronary heart disease: The dal-vessel randomized clinical trial. *Eur Heart J*. 2012;33:857-865
 14. Fayad ZA, Mani V, Woodward M, Kallend D, Abt M, Burgess T, Fuster V, Ballantyne CM, Stein EA, Tardif JC, Rudd JH, Farkouh ME, Tawakol A.

- Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-plaque): A randomised clinical trial. *Lancet*. 2011;378:1547-1559
15. Spieker LE, Sudano I, Hurlimann D, Lerch PG, Lang MG, Binggeli C, Corti R, Ruschitzka F, Luscher TF, Noll G. High-density lipoprotein restores endothelial function in hypercholesterolemic men. *Circulation*. 2002;105:1399-1402
 16. Cannon CP, Shah S, Dansky HM, Davidson M, Brinton EA, Gotto AM, Stepanavage M, Liu SX, Gibbons P, Ashraf TB, Zafarino J, Mitchel Y, Barter P. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med*. 2010;363:2406-2415
 17. Nicholls SJ, Brewer HB, Kastelein JJ, Krueger KA, Wang MD, Shao M, Hu B, McErlean E, Nissen SE. Effects of the cetp inhibitor evacetrapib administered as monotherapy or in combination with statins on hdl and ldl cholesterol: A randomized controlled trial. *JAMA*. 2011;306:2099-2109
 18. Voight BF, Peloso GM, al. e. Plasma hdl cholesterol and risk of myocardial infarction: A mendelian randomisation study. *Lancet*. 2012;published online May 17 2012
 19. Khera AV, Cuchel M, de la Llera-Moya M, Rodrigues A, Burke MF, Jafri K, French BC, Phillips JA, Mucksavage ML, Wilensky RL, Mohler ER, Rothblat GH, Rader DJ. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med*. 2011;364:127-135
 20. Besler C, Heinrich H, Rohrer L, Doerries C, Riwanto M, Shih DM, Chroni A, Yonekawa K, Stein S, Schaefer N, Mueller M, Akhmedov A, Daniil G, Manes C, Templin C, Wyss C, Maier W, Tanner FC, Matter CM, Corti R, Furlong C,

- Lusis AJ, Eckardstein Av, Fogelman AM, Lüscher TF, Landmesser U. Mechanisms underlying adverse effects of hdl on enos-activating pathways in patients with coronary artery disease. *J Clin Invest.* 2011;121(7)::2693-2708
21. Sorrentino SA, Besler C, Rohrer L, Meyer M, Heinrich K, Bahlmann F, Müller M, Horvath T, Doerries C, Heinemann M, Flemmer S, Markowski A, Manes C, Bahr MJ, Haller H, Von Eckardstein A, Drexler H, Landmesser U. Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy. *Circulation.* 2010;121:110-122
 22. Vaisar T, Pennathur S, Green PS, Gharib SA, Hoofnagle AN, Cheung MC, Byun J, Vuletic S, Kassim S, Singh P, Chea H, Knopp RH, Brunzell J, Geary R, Chait A, Zhao XQ, Elkon K, Marcovina S, Ridker P, Oram JF, Heinecke JW. Shotgun proteomics implicates protease inhibition and complement activation in the antiinflammatory properties of hdl. *J Clin Invest.* 2007;117:746-756